



TITLE:

# The Chemistry on Diterpenoids in 1967

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# The Chemistry on Diterpenoids in 1967

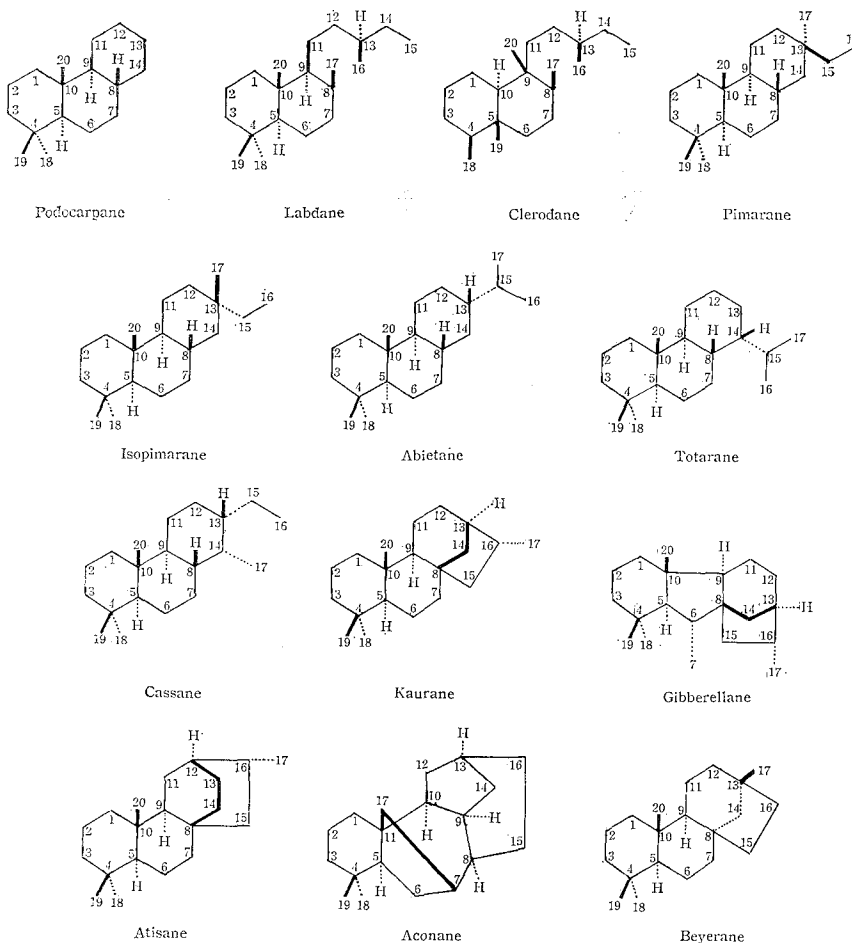
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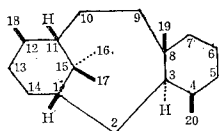
## I. INTRODUCTION

One of the authors (E.F.) has published the reviews of the chemistry on diterpenoids in 1964,<sup>1)</sup> 1965<sup>2)</sup> and 1966.<sup>3)</sup> This review deals with an outline of the chemical works on diterpenoids in 1967.

The classification consists of podocarpane, labdane, clerodane, pimarane,



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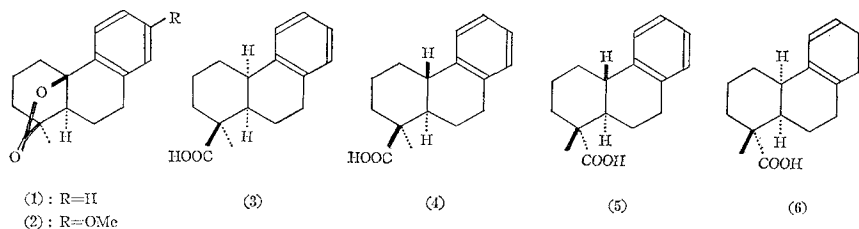


Taxane

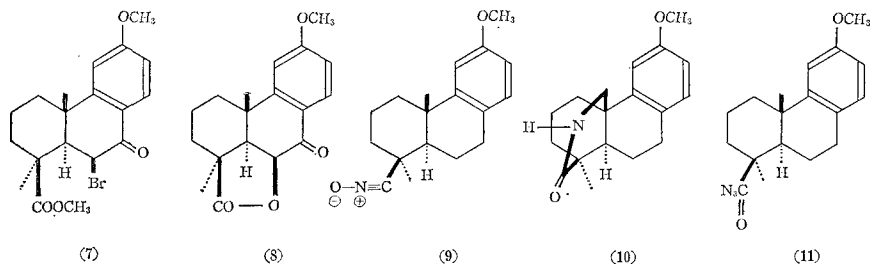
isopimarane, abietane, totarane, cassane, kaurane, gibberellane, atisane, aconane, beyerane, taxane, and the others, in accordance with a proposal for systematic nomenclature subscribed to by most workers in this area.<sup>4)</sup>

## II. PODOCARPANE DERIVATIVES

Chakravarty *et al.*<sup>5)</sup> synthesized lactones **1**<sup>6)</sup> and **2** and four possible epimeric acids **3**, **4**,<sup>7)</sup> **5** and **6**.

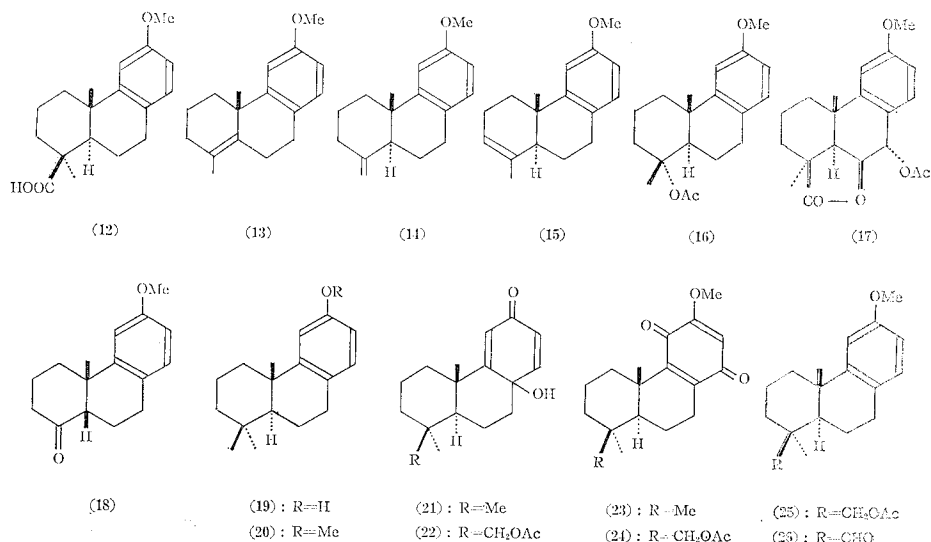


Wheeler *et al.*<sup>8)</sup> studied conformations of some derivatives of podocarpic acid. They proposed using NMR data that the bromine in **7** is  $\beta$  and the ring B is distorted to a half-boat form, and suggested a mechanism of the formation of lactone **8** from **7** by heating with collidine. Just and Dahl<sup>9)</sup> obtained a stable O-methylpodocarpitrile oxide (**9**) by oxidation of podocarpinal *syn*-oxime with  $\text{Pb}(\text{OAc})_4$ . Irradiation of the nitrile oxide gave **10**<sup>10)</sup> that was identical with the irradiation product of the azide **11**.



Bennett and Cambie<sup>11)</sup> studied the oxidation of O-methylpodocarpic acid **12** with  $\text{Pb}(\text{OAc})_4$ , and yielded alkenes **13**, **14** and **15**, and acetates **16** and **17**. Oxidation of alkenes mixture with permanganate or Lemieux-Johnson's reagent gave **18**.

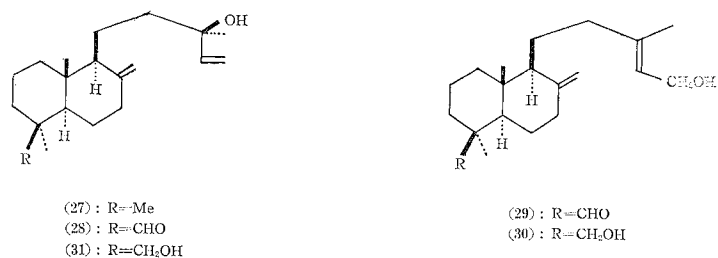
Burkinshaw and Davis<sup>12)</sup> studied the peracid oxidation of phenol **19** and its methyl ether **20** and reported the formation of *p*-benzoquinones, 4-hydroxycyclohexa-2,5-diones and acetates *etc.* (**21**~**26**). Enzell<sup>13)</sup> studied mass spectra using deuterium labelling of podocarpa-8,11,13-triene.



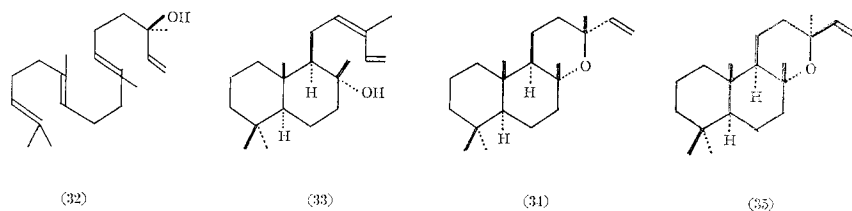
## III. LABDANE DERIVATIVES

From the resin of *Pinus sibirica*, agathadienediol was isolated by Russian workers.<sup>14)</sup>

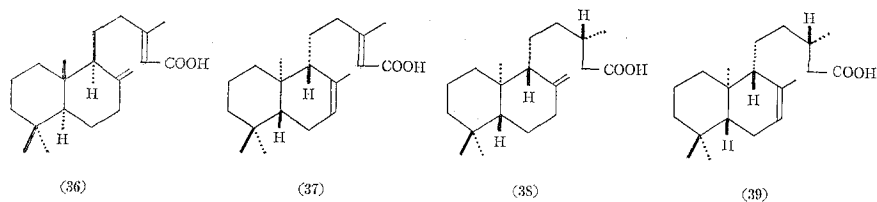
Mangoni and Caputo<sup>15)\*</sup> isolated manool (27), torulosal (28), isoagatholal (29), agathadiol (39) and torulosol (31) from *Cupressus sempervirens* resin. Grant *et al.*<sup>47)</sup> isolated manool (27) and torulosol (31) from *Dacrydium bidwillii*.



Norin and Kimland<sup>16)</sup> isolated (–)-geranyllinalool (32), abienol (33), manoyl oxide (34) and 13-*epi*manoyloxide (35) from the oleoresin of *Picea abies*. Corbett and Smith<sup>46)</sup> isolated manoyl oxide (34) from the volatile oil of *Dacrydium colensoi*.

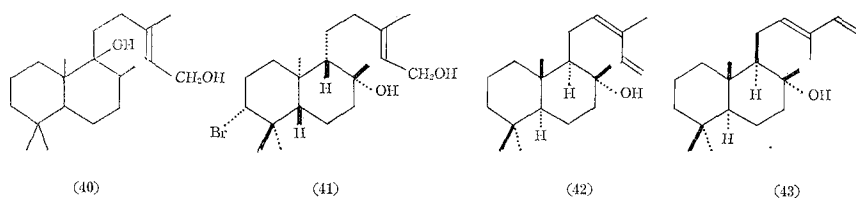


\* See also section V.



Ekong and Okogun<sup>17)</sup> isolated four diterpenes from *Oxystigma oxyphyllum* and gave them the structures 36~39.

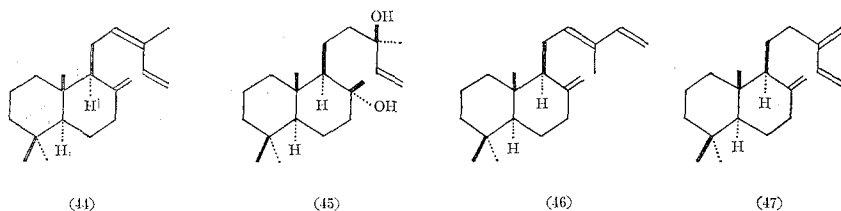
Sandermann, Bruns *et al.*<sup>18)</sup> also isolated eperuic acid (38) and another acid 37 from the heartwood of the same plant. The structure of peregrinol, a diterpene from *Marrubium peregrinum*, was proposed as 40 by Russian workers.<sup>19,20)</sup>



Two naturally occurring bromo-compounds, aplysin and aplysinol have been isolated from *Aplysia kurodai*, and their structures have already been established.<sup>21)</sup> The third minor bromo-compound, aplysin-20 was isolated and the structure 41 was shown to be in agreement with X-ray analysis, and chemical and spectral evidence.<sup>22)</sup>

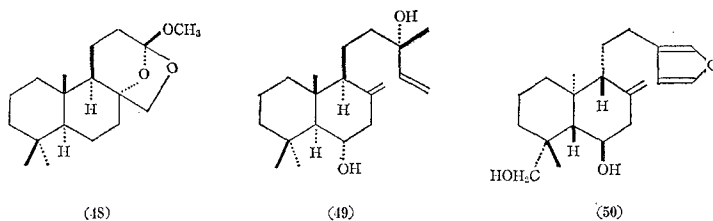
Mills<sup>23)</sup> converted abienol (42) into *trans*-abienol (43) by mercuric acetate.

Carman and Dennis<sup>24)</sup> converted abienol (42) into *cis*-biformene (44) by dehydration with POCl<sub>3</sub> in pyridine at 0°. They also carried out the similar dehydration with manool (27) and sclareol (45), and got *cis*- and *trans*-biformene (46) and sclarene (47). The acid-catalyzed dehydration was also tried on manool. The same authors<sup>25)</sup> made trichloro-derivatives from sclareol (45), manool (27) and manoyl oxides, 34 and 35, and studied their stereochemistry.



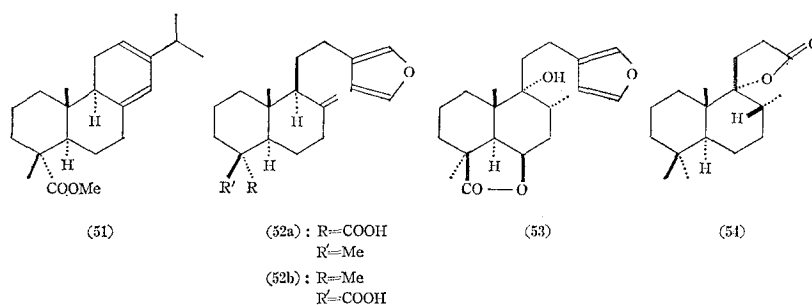
Schmidt *et al.*<sup>26)</sup> reported that a diterpene diol previously isolated was 13-epitorulosol. Demole and Wuest<sup>27)</sup> synthesized a powerful amber-like odorous compound 48 from manool derivative. Popa and Titov<sup>28)</sup> investigated peracids oxidation of sclareol.

Overton and Renfrew<sup>29)</sup> reported the configuration at C-13 in labdanolic and eperuic acids to be R, but later they corrected it to S, which coincided with Henrick and Jefferies' assignment.

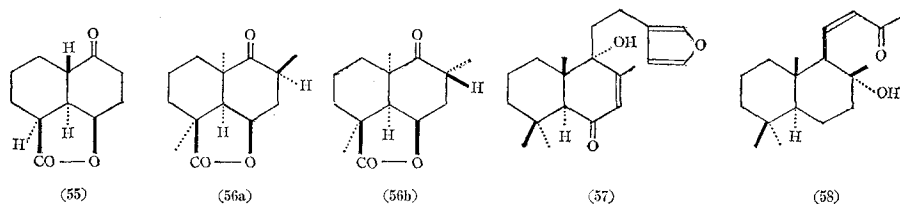


Carman<sup>30)</sup> suggested 13 S configuration **49** for larixol against Norin *et al.*<sup>31)</sup> and Sandermann and Bruns.<sup>32)</sup> A major diterpenoid, psiadiol, was isolated from the leaves of *Psiadia altissima* and given the structure **50** by Canonica *et al.*<sup>33)</sup>

Pelletier *et al.*<sup>34a)</sup> converted methyl levopimarate (51) into antipodal polyalthic acid (52a). Anti-daniellic acid (lambertianic acid) (52b) and its methyl ester were isolated from the oleoresin of *Pinus sibirica*.<sup>34b)</sup>



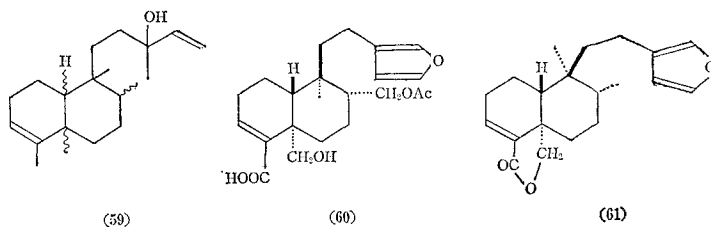
Fetizon *et al.*<sup>35)</sup> studied the stereochemistry of marrubiin and presented a conclusion that marubiin should be represented as **53** including absolute configuration. They modified the  $8\beta$  stereochemistry of isoambreinolide into  $8\alpha$  as shown in **54**. The same conclusion on marrubiin was presented by McCrindle *et al.*<sup>36a)</sup> Mangoni and Adinolfi<sup>36b)</sup> also presented a paper supporting the stereochemistry **54** for isoambreinolide. Wheeler *et al.*<sup>37)</sup> converted keto-lactone **55** into **56a** and **56b**, neither of which was not identical with the trimethyl keto-lactone analogue derived from marrubiin.



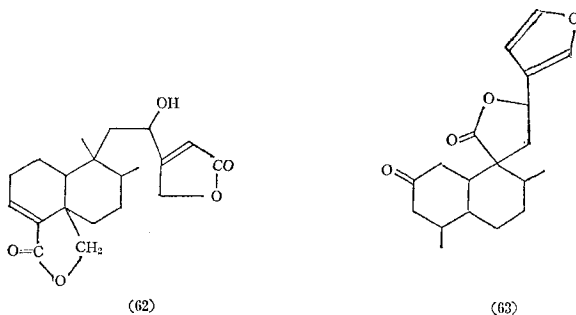
Solidagenone (57) isolated from roots of *Solidago canadensis* was related with marrubiin (53) by McCrindle *et al.*<sup>38)</sup> A neutral hydroxy ketone 58 was isolated and characterized.<sup>39)</sup>

## IV. CLERODANE DERIVATIVES

The structure of plathyterpol, a liquid diterpene from the heartwood of *Plathymenia reticulata*, was proposed as **59** by King and Rodrigo.<sup>40)</sup> Jefferies and Payne<sup>41)</sup> reported the isolation and characterization of diterpenoids of the enantio-labdane type from *Dodonaea attenuata*. The ether extract gave clerodane derivatives: acetoxy-hydroxy-acid **60** and lactone **61**.



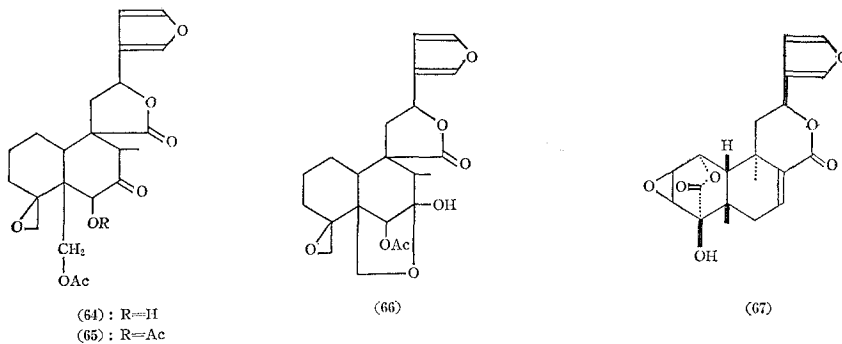
Pinkney and Simpson<sup>42)</sup> isolated a new neutral diterpene, olearin from *Olearia heterocarpha* and suggested structure **62** on the basis of chemical and spectroscopic evidence.



Cham *et al.*<sup>43)</sup> yielded a new furanoid norditerpene, crotonin (**63**) from the extract of the leaves and twigs of *Croton lucidus*.

Brieskorn and Pfeufer<sup>44)</sup> isolated three new diterpenoids from *Teucrium polium*. The major bitter principle was pikropolin, the structure of which was proposed as **64**.

They also isolated other two related compounds (**65** and **66**) and some un-

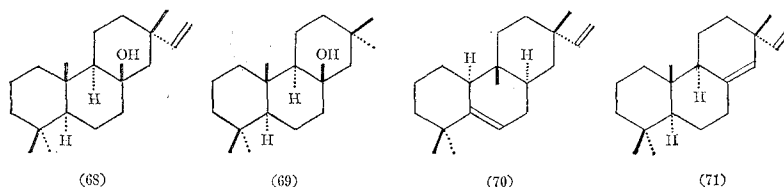


identified compounds.

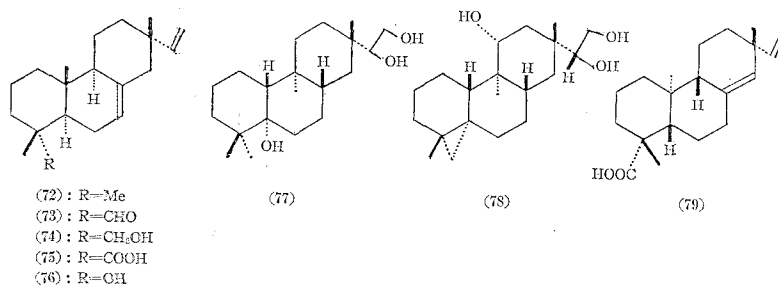
Nakanishi *et al.*<sup>45)</sup> proposed the chemical structure 67 for fibraurin and assigned the structure of 6-hydroxyfibraurin to a minor component. They were isolated from *Fibraurea chloroleuca*.

## V. PIMARANE AND ISOPIMARANE DERIVATIVES

Corbett and Smith<sup>46)</sup> isolated a new diterpene alcohol from the volatile oil of *Dacrydium colensoi* and clarified its structure to be represented as 68 by its chemical conversion into the known noralcohol 69. They also isolated rimuene (70) and sandaracopimaradiene (71) besides some other diterpenoids.\*

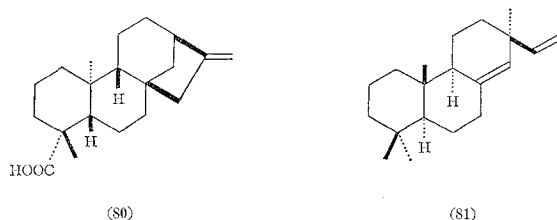


Grant *et al.*<sup>47)</sup> isolated isopimara-7, 15-diene (72), isopimaradienal (73), isopimaradienol (74), isopimaric acid (75), and 18-nor-isopimaradiene-4 $\alpha$ -ol (76) from *Dacrydium bidwillii*, besides some labdane derivatives.\*\*



McCrindle, Overton *et al.*<sup>48)</sup> published a full paper, the preliminary communications of which were reported already in 1964<sup>1)</sup> and 1966<sup>3)</sup>; the structures for erythroxytriol P and erythroxytriol Q obtained from *Erythroxyylon monogynum* were suggested on the basis of spectroscopic and chemical evidence as 77 and 78, respectively.

Shibata *et al.*<sup>49)</sup> isolated a new diterpene carboxylic acid, that is, *ent*-pimara-



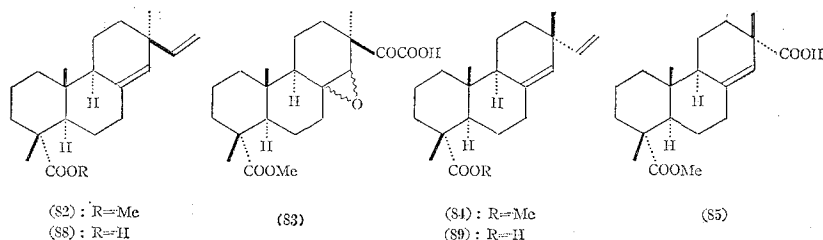
\* See also Sections III and VIII.

\*\* See Section III.

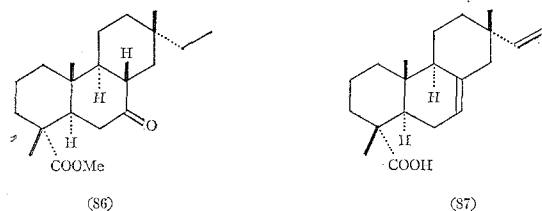


8 (14), 15-dien-19-oic acid (79) from the roots of *Aralia cordata*. They also recognized the presence of *ent*-kaur-16-en-19-oic acid (80) or its antipode in the root of the same plant by VPC. Further VPC test with methylated products of the crude ethereal extracts showed the presence of 79 and 81 (or its antipode) in the same source.

ApSimon *et al.*<sup>50)</sup> investigated the use Lemieux- von Rudloff technique for oxidation of the vinyl groups in methyl pimarate (82) and methyl sandaracopimarate (84). An unexpected epoxy acid 83 was obtained from 82, whereas the expected acid 85 was yielded from 84.

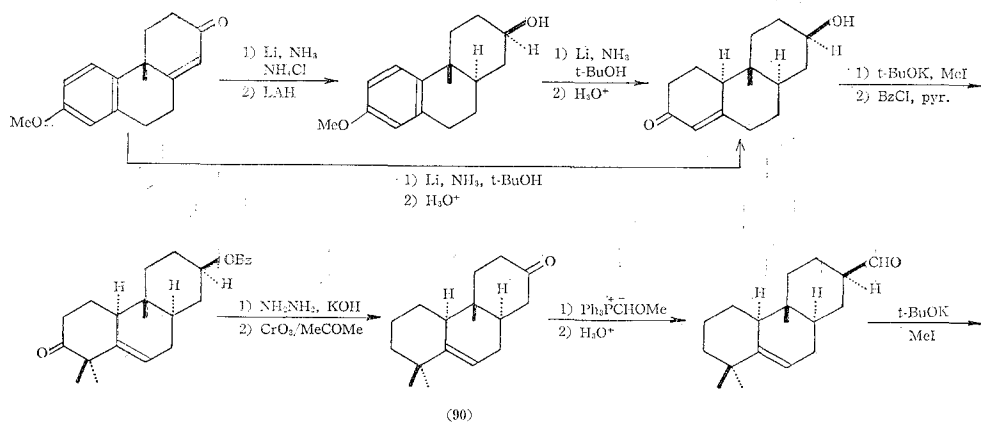


Bose *et al.*<sup>51)</sup> studied the ORD curve and mass spectrum of the keto-ester 86 obtained from methyl dihydroisopimarate and clarified the keto group to be present at C-7. This was also confirmed by the mass spectrum of the deuterated ketoester. On the basis of these data it was concluded that the nuclear double bond is in the 7 (8) position in isopimaric acid (87).



Kuthan *et al.*<sup>52)</sup> investigated the partial dehydrogenation and reduction of sandaracopimaric acid (89) and pimaric acid (88).

Ireland and Mander<sup>53)</sup> published a full paper of the total synthesis of ( $\pm$ )-



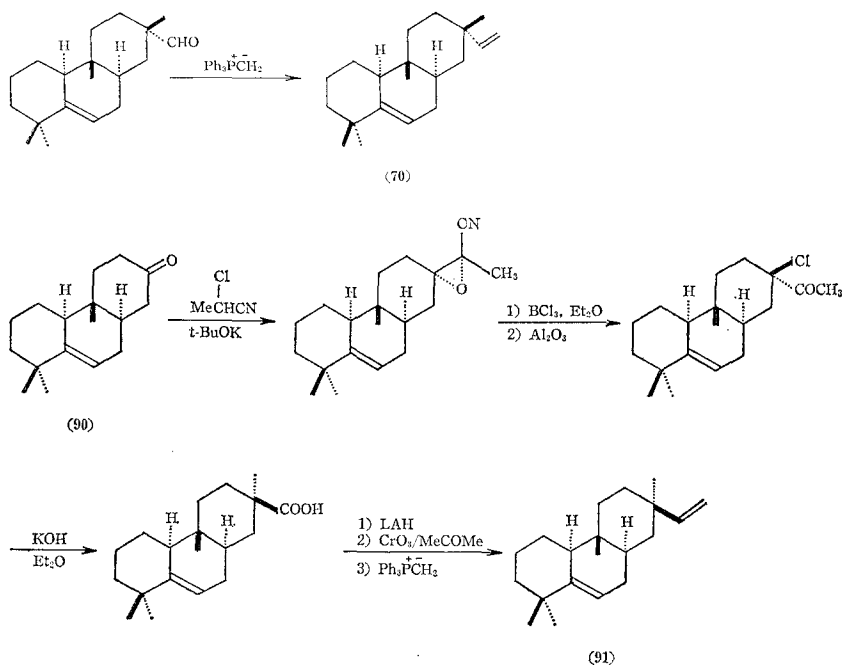
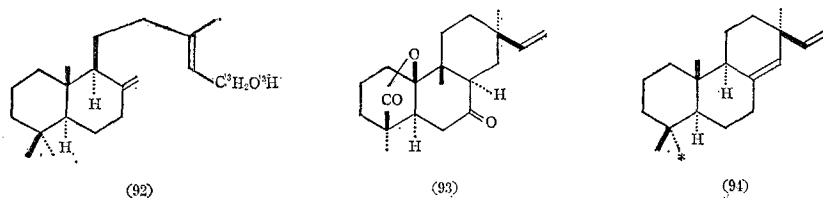


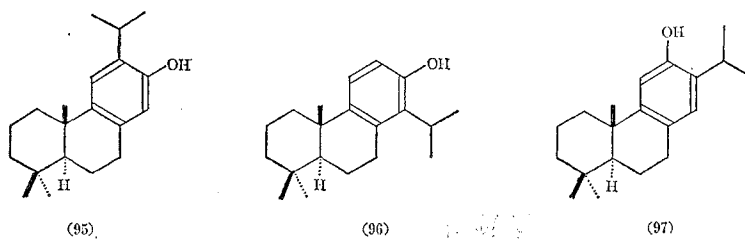
Chart 1

rimuene (70) and (±)-13-*epi*-rimuene (91). The routes are shown in Chart 1.

Tritium labelled alcohol 92, prepared from sclareol, was fed to *Tricothecium roseum* by Hanson and Achilladelis.<sup>54</sup> Isolation of rosenonolactone (93) showed an incorporation of 0.13%. The labelled hydrocarbon 94, prepared from methyl pimarate was fed to *T. roseum*. However, no consistent incorporation was observed.



## VI. ABIETANE\* AND TOTARANE DERIVATIVES



\* See also Sections VIII, refs. 90 and 85.

The structure **95** was assigned to semperviol by Mangoni and Caputo.<sup>15,55)</sup> Totarol (**96**) and ferruginol (**97**) together with semperviol were isolated from *Cupressus sempervirens* resin.<sup>15)</sup>

Racemic semperviol (**95**) was total-synthesized by Mangoni and Caputo<sup>56)</sup>

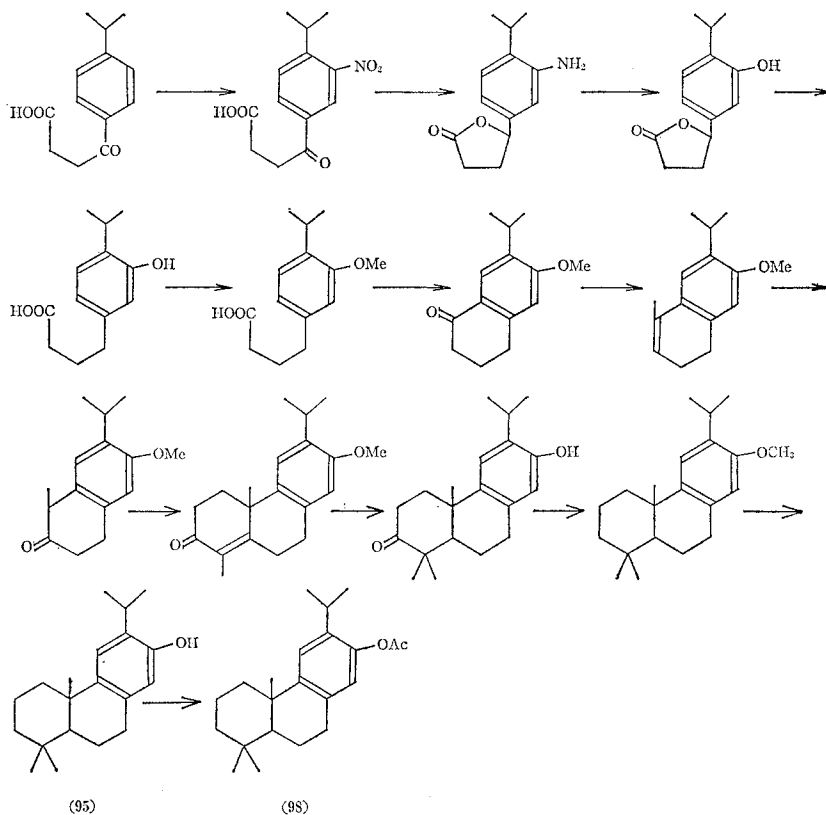


Chart 2

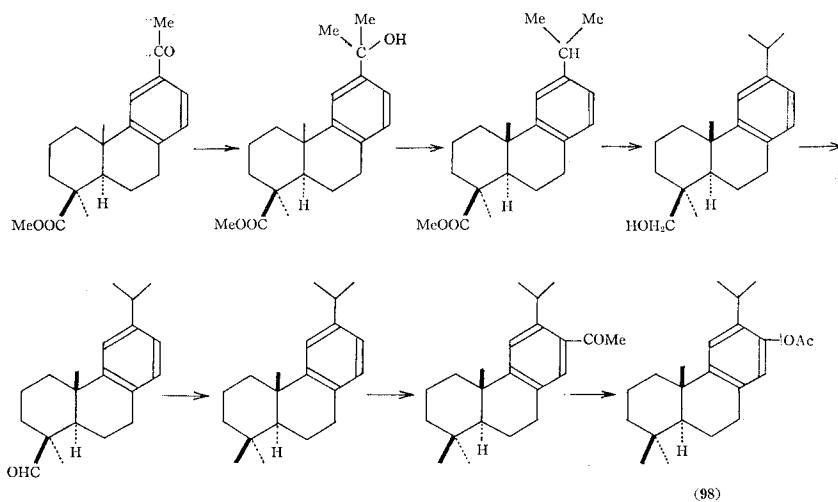


Chart 3

and identified as its acetate **98** as shown in Chart 2.

Another total synthesis of racemic semperviolol acetate (**98**) was reported by Ghatak and Chatterjee.<sup>57)</sup> The route is shown in Chart 3.

The total synthesis of racemic methyl dehydroabietate (**99**) was carried out by Meyer and Sigel<sup>58)</sup> as shown in Chart 4.

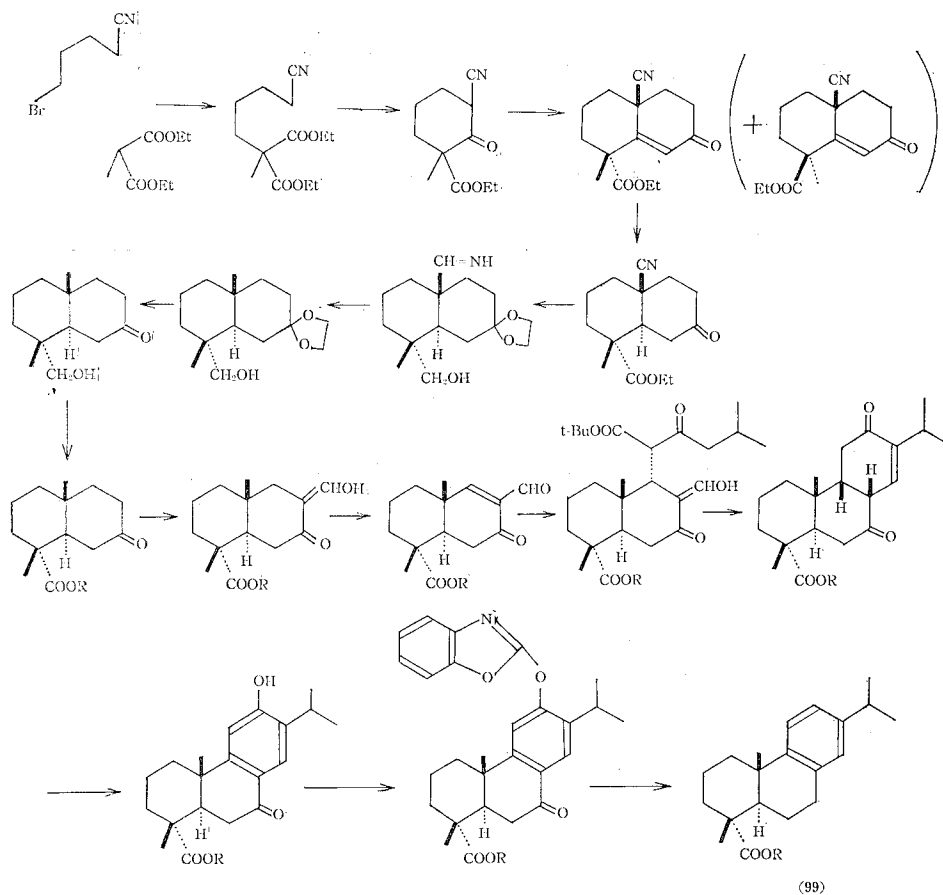
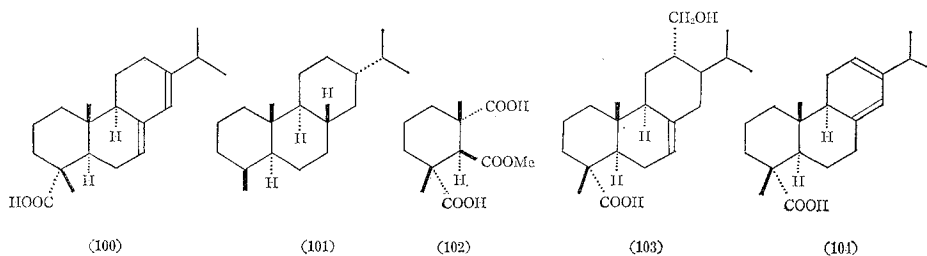
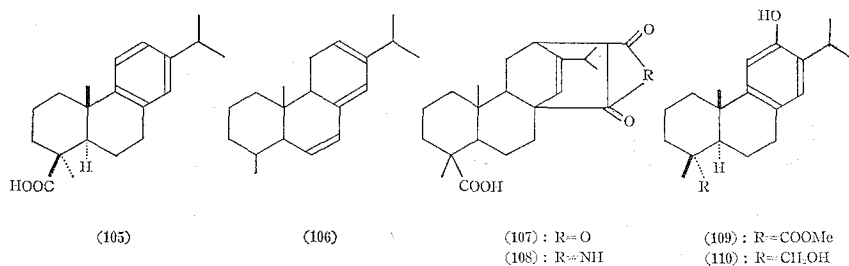


Chart 4

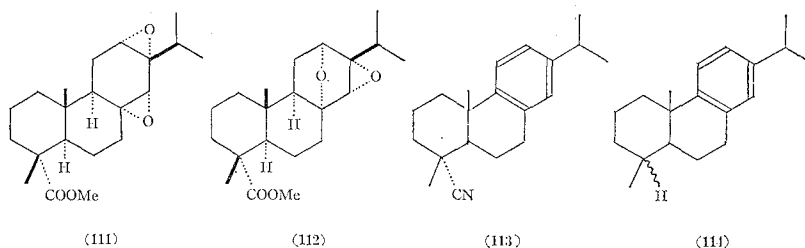
Jensen and Johnson<sup>59)</sup> carried out a three step synthesis of fichtelite (**101**) from abietic acid (**100**). The tricarboxylic acid named *meso-trans*-2-carboxy-methyl-1, 3-dimethylcyclohexane-1, 3-dicarboxylic acid (**102**), originally derived from abietic acid, was synthesized stereoselectively by Raphael *et al.*<sup>60)</sup> 12 $\alpha$ -



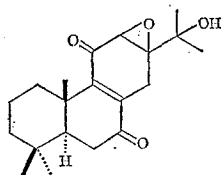
Methyl dehydroabietate and methyl 12-bromodehydroabietate were oxidized with  $\text{KMnO}_4$  in the presence of  $\text{MnSO}_4$  in pyridine at  $85^\circ$  to yield 7-oxo products. The alkaline hydrolysis of the materials and products was investigated.<sup>63)</sup> 4-Epidehydroabietic acid (**105**) was isolated from the oleoresin of *Callitris columellaris* by Carman and Deeth.<sup>64)</sup> Thermal decomposition of an adduct of maleic anhydride to levopimaric acid was investigated, and succinic acid, its anhydride, and probably **106** were obtained.<sup>65)</sup> Some new derivatives of maleopimaric acid (**107**), e.g. mono acid chloride, mono methyl ester, maleopimarimide (**108**), and its N-substituted derivatives, were prepared and characterized by Schuller and Lawrence.<sup>66)</sup>



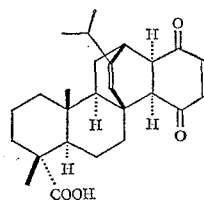
Hudec and Kelly<sup>68)</sup> suggested structure **111** for the dioxide product resulting from heating of levopimaric acid peroxide, against structure **112** proposed by Lawrence *et al.*<sup>69)</sup>



(533)



(115)

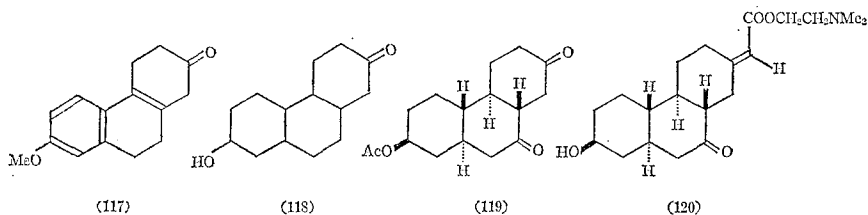


(116)

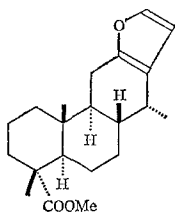
Structure of callicarpone, a fish-killing component of *Callicarpa candicans*, was determined as **115**.<sup>71)</sup> The configuration of the adduct of *p*-benzoquinone to levopimaric acid was established as **116**, whose various reduction products were characterized.<sup>72)</sup> Some hydrophenanthrene derivatives were synthesized for the pre-investigation of the synthesis of tanshinones.<sup>73)</sup>

## VII. CASSANE DERIVATIVES

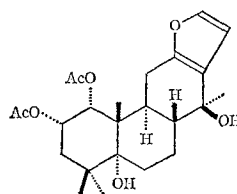
Daum *et al.*<sup>74)</sup> used methoxyhydrophenanthrone **117** as a key intermediate, and synthesized four possible ring-A-aromatic 7-methoxyoctahydrophenanthrols and perhydrophenanthrones **118** with *cis-anti-trans*, *trans-anti-cis*, and *trans-anti-*



*trans* configuration. They<sup>75)</sup> synthesized racemic 17, 18, 19, 20-tetranorcassaine (**120**) *via* **119**. Spencer *et al.*<sup>76)</sup> carried out the stereoselective total synthesis of racemic methyl vinhaticoate (**121**), and determined the stereochemistry of the secondary methyl group at C-14. Ferguson *et al.*<sup>77)</sup> isolated  $\epsilon$ -caesalpin from the seeds of *Caesalpinia bonducella* and assigned the structure to it and confirmed it by X-ray analysis. The structure and absolute configuration were determined as **122**.



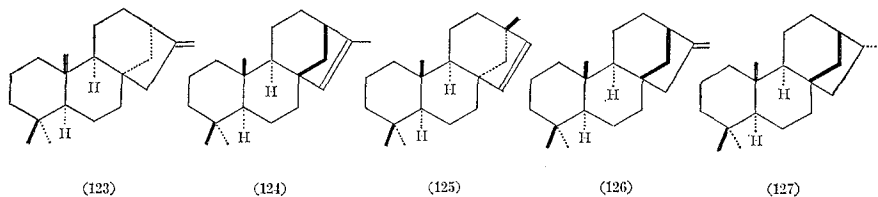
(121)



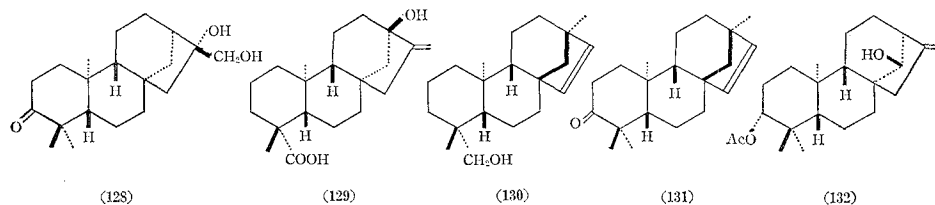
(122)

## VIII. KAURANE AND BEYERANE DERIVATIVES

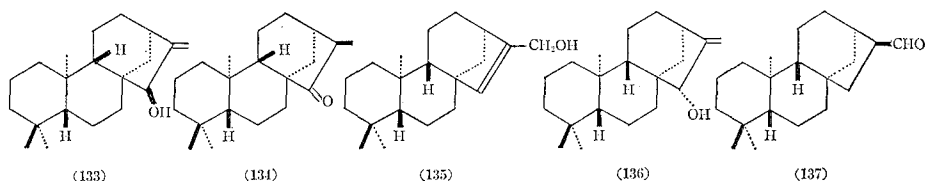
Phyllocladene (**123**) and isokaurene (**124**) were isolated from the volatile oil of *Dacrydium colensoi*.<sup>46)</sup> Conversion of hibaene (**125**) into kaurene (**126**), iso-



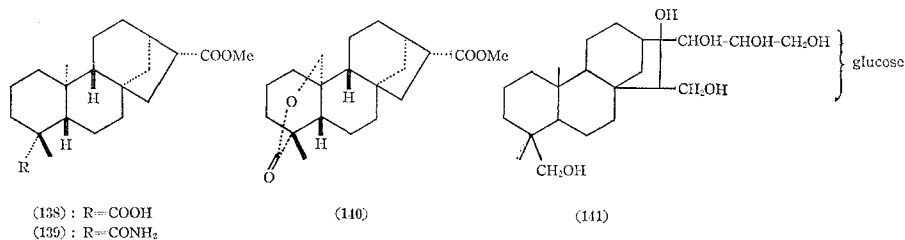
kaurene (124), and kaurane (127) was carried out by Kitahara and Yoshikoshi *et al.*<sup>78)</sup> The structure of abbeokutone, a diterpene from *Didymosalphinx abbeokutae*, was clarified as 128 by Taylor.<sup>79)</sup> Steviol (129) was converted into erythroxylyol A (monogynol) (130) and the reverse conversion of 3-oxo-*ent*-hibaene (131) into an *ent*-kaurene derivative 132 was also presented by Hanson.<sup>80)</sup> The stereochem-



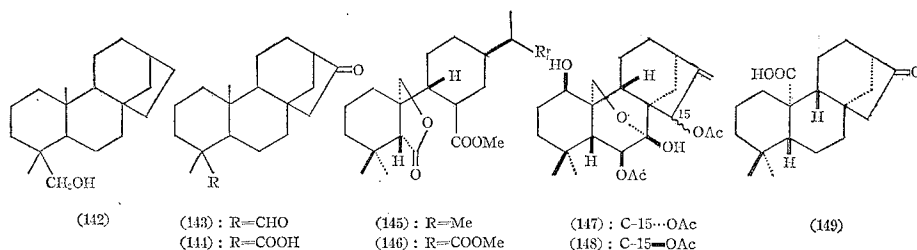
istry of some reactions at C-16 in *ent*-kaurene was clarified by the same author.<sup>81)</sup> The mechanism of garryfoline-cuauchichicine rearrangement was investigated using the epimeric *ent*-kauren-15-ols as models. The 15 $\beta$ -ol 133 was shown to rearrange rapidly in mineral acid at room temperature to 16R-*ent*-kauran-15-one (134) by a 15,16-hydride shift. The 15 $\alpha$ -ol is stable under these conditions. Under the same conditions, *ent*-kaur-15-en-17-ol (135) gave the allylic isomer, *ent*-kaur-16-en-15 $\alpha$ -ol (136), but under more forcing conditions it yielded 16S-*ent*-kauran-17-al (137).<sup>82)</sup>



Amide 139, obtained from 138, was treated with lead tetracetate and I<sub>2</sub> and photolyzed to give lactone ester 140.<sup>83)</sup>

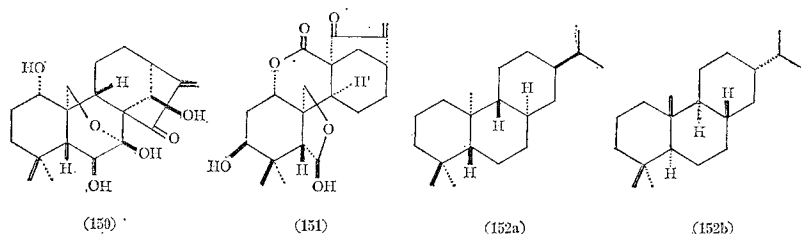


The structure 141 of corymbosin, a glucoside from *Turbina corymbosa*, was proposed<sup>84)</sup>; corymbositin, the aglucone, was converted into alcohol 142, keto-



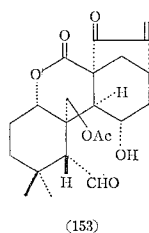
aldehyde 143, and keto-carboxylic acid 144.

Acyloin condensation with  $\gamma$ -lactone esters—that is, 145 and 146 which were derived from enmein (151)—was investigated by Fujita *et al.*<sup>85)</sup> The structure and stereochemistry of trichokaurin from *Isodon trichocarpus* were studied and formula 147 was first proposed by Fujita *et al.*,<sup>86)</sup> but soon later, the stereochemistry of acetoxy-group at C-15 was revised to 148 by themselves.<sup>87)</sup> Trichokaurin (148) was chemically converted into the known keto-carboxylic acid 149 by Fujita *et al.*<sup>88)</sup> since the acid 149 had been converted into *ent*-kaurene, atisine, garryine, and veatchine, this transformation constituted the chemical conversion of trichokaurin into *ent*-kaurene and those diterpene alkaloids. Fujita *et al.*<sup>89)</sup> isolated a new diterpenoid, oridonin, from *Isodon* species and clarified the structure and absolute configuration as shown in formula 150.



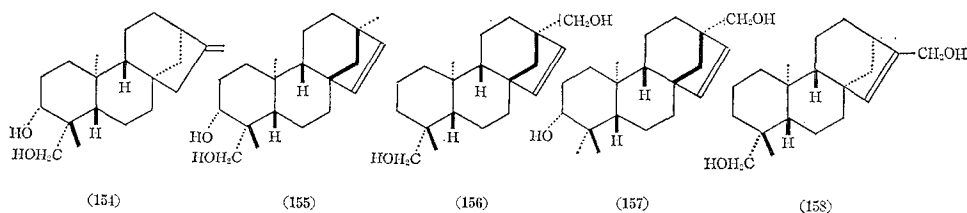
Enmein (151) was converted into a hydrocarbon 152 a,<sup>90)</sup> which is enantiomer of the hydrocarbon 152 b derived from abietic acid (100). The latter 152 b was named abietane, and the former 152 a was named *enantio*-abietane by Fujita *et al.*<sup>90)</sup> A detailed full paper on the isolation of pure enmein and enmein 3-acetate from the leaves of *Isodon japonicus* was published.<sup>91a)</sup> The component of the stems of *Isodon trichocarpus* was investigated, and the isolation of enmein and oridonin (150) was reported.<sup>91b)</sup>

Kubota and Kubo<sup>92)</sup> elucidated the structure and absolute configuration of isodonal, a new bitter principle of *Isodon japonicus*, as shown in formula 153.

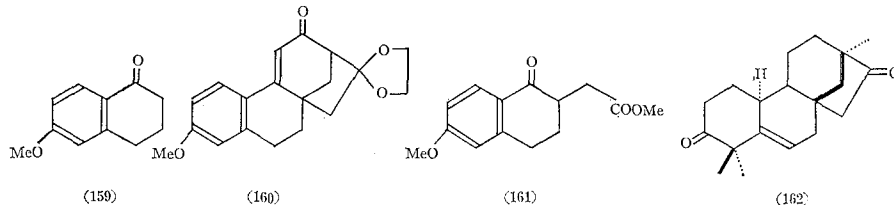




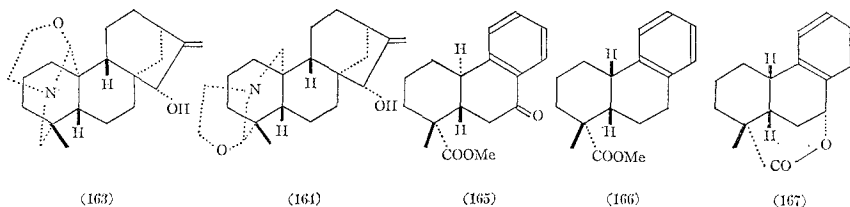
Seven species of reportedly poisonous Ericaceous plants were screened by thin-layer chromatography in order to detect the presence of the grayanotoxins. Grayanotoxin I was isolated and identified from one of the species. Five of the plants screened were found to contain grayanotoxin I, whereas grayanotoxins II and III were not detected.<sup>93)</sup> From the neutral fraction of the saponified leaf wax of *Helichrysm dendrodeum* (Australian Compositae), *ent*-16-kaurene-3 $\beta$ , 19-diol (154), *ent*-15-beyerene-3 $\beta$ , 19-diol (155), and *ent*-15-beyerene-17, 19-diol (156) were isolated.<sup>94)</sup> Among these substances, 155 is a new compound. In addition, *ent*-15-beyerene-3 $\beta$ , 17-diol (157) and *ent*-15-kaurene-17, 19-diol (158) were isolated and characterized.



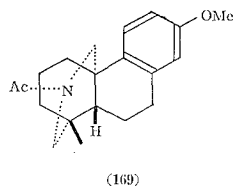
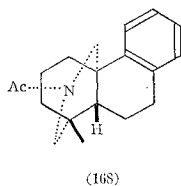
6-Methoxy-1, 2, 3, 4-tetrahydronaphthalenone (159) was converted into 160.<sup>95)</sup> Similarly, 161, derived from 159, was converted into *rac*-3, 16-dioxo-20-norbeyer-5-ene (162).<sup>96)</sup>



An elegant total synthesis of *rac*-veatchine (163) and *rac*-garryine (164) had been accomplished by Nagata *et al.*<sup>97)</sup> Now, the full detailed paper was published.<sup>98)</sup>



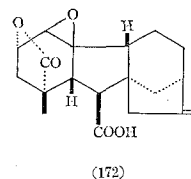
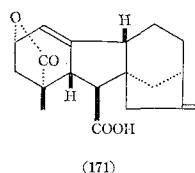
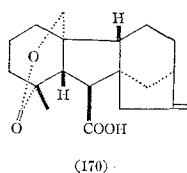
Tahara *et al.* carried out the chemical conversion of abietic acid (100) into tricyclic 20-norditerpenes with aromatic ring C<sup>99)</sup>—*e.g.* 165, 166, 167 *etc.*—and a basic skeleton compound 168.<sup>100)</sup> Subsequently, they published the full paper of the chemical conversion of abietic acid (100) into 169,<sup>101)</sup> the short communication of which had been reported.<sup>102)</sup> Since compound 169 has been converted into garryine, veatchine and atisine, and abietic acid has been synthesized, this conversion constitutes a formal total synthesis of these diterpene alkaloids.



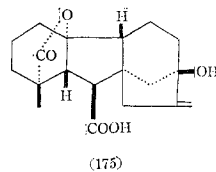
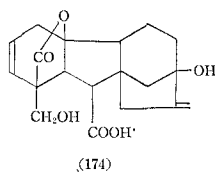
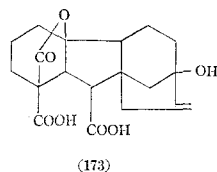
## IX. GIBBERELLANE DERIVATIVES

Several reviews concerning or including gibberellins were published.<sup>103-106)</sup>

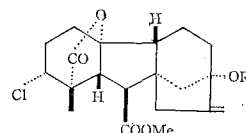
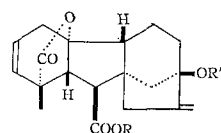
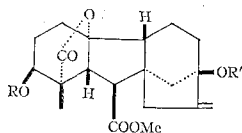
High resolution mass spectra of 12 kinds of gibberellin homologue methyl esters were taken and analyzed.<sup>107)</sup> On the basis of spectroscopic and chemical properties, structure **170** was assigned to gibberellin A<sub>15</sub>, a new metabolite of *Gibberella fujikuroi*, by Hanson.<sup>108)</sup> Two new compounds were isolated from culture filtrates of *Gibberella fujikuroi*, one of which was shown to have structure **171**, whilst the other was provisionally assigned structure **172**.<sup>109)</sup> Structures of



new gibberellins in immature seeds of *Canavalia gladiata* were studied and assigned to *Canavalia* gibberellin-I (**173**) and C-g-II (**174**).<sup>110)</sup> Gibberellins in immature seeds of *Pharbitis nil* were investigated, and gibberellin A<sub>3</sub> and a new C-19 gibberellin (tentative name: *Pharbitis* gibberellin) (**175**) were found.<sup>111)</sup>



During the course of the chemical conversion from gibberellin A<sub>1</sub> methyl ester (**176**) to gibberellin A<sub>5</sub> (**177**), a mixture of monotosylate **178** and ditosylate **179** was boiled with collidine, and then hydrolyzed with methanolic sodium hydroxide solution. This procedure gave gibberellin A<sub>5</sub> (**177**) (20%) accompanied by three by-products **180**, **181**, and **182** (isolated as methyl esters). Now, the solvolysis of



the tosylate 183, that is, gibberellin A<sub>5</sub> methyl ester toluene-*p*-sulfonate, was studied by MacMillan and Pryce.<sup>112)</sup> The epimerisation of 3-axial to 3-equatorial hydroxy group in lactone type C-19 gibberellins was investigated by the same authors,<sup>113)</sup> who supported the mechanism by Cornforth shown in Chart 5.

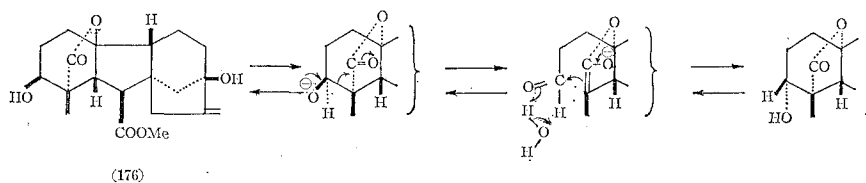
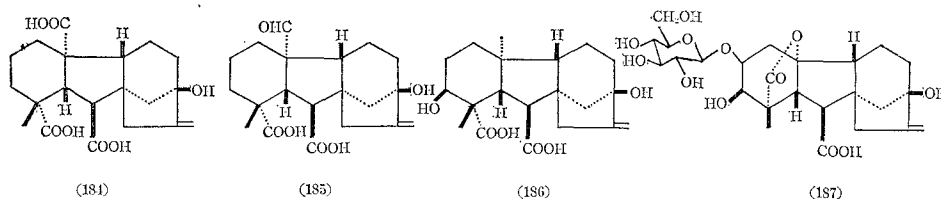
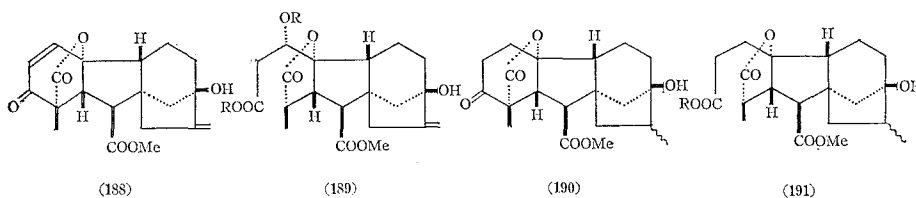


Chart 5

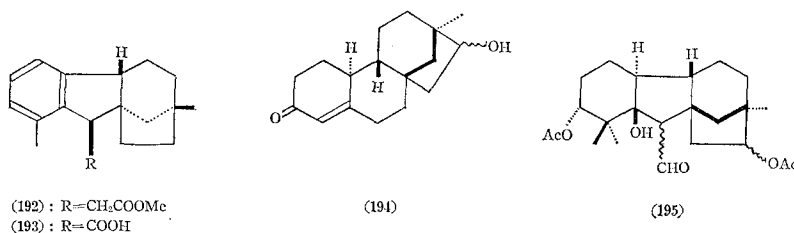
They<sup>114)</sup> also isolated a new gibberellin from the seed of *Phaseolus multiflorus* and named gibberellin A<sub>17</sub>. The structure 184 was assigned to this gibberellin. Gas-liquid chromatography of the methylated fraction of acids from immature



seeds of *Phaseolus multiflorus* showed the presence of gibberellins A<sub>17</sub> (184) and A<sub>5</sub> (177), and the mass spectrometry recognized the presence of Bamboo gibberellin (185). The investigation of the green plant showed the presence of Bamboo gibberellin (185), Lupinus I (186), and A<sub>17</sub> (184).<sup>115)</sup> The 13-hydroxylation in the



biogenesis was discussed in contrast to the fungal biogenesis.<sup>115)</sup> From immature fresh fruit of *Phaseolus coccineus* var. *coccineus*, *Phaseolus*  $\epsilon$ , a gibberellin glucoside, was isolated, and structure 187 was assigned to it.<sup>116)</sup> It was found that some 3-oxo-derivatives of gibberellins undergo readily the retro-Claisen cleavage of ring A. Thus, ketone 188 in alcoholic solution in the presence of



catalytic amounts of alkali opened ring A under mild conditions to give alkoxy lactone diester **189**.<sup>117)</sup> Similarly, ketone **190** gave **191**.

The C-6 epimer of *rac*-desoxo-gibberic acid (**193**) was synthesized by the application of the Barbier-Wieland degradation of an ester **192**.<sup>118)</sup> A racemic gibberellane derivative **195** was converted from **194** *via* several steps.<sup>119)</sup> *rac*-13-Deoxyepiallo-gibberic acid methyl ester norketone (**196**) was synthesized<sup>120)</sup> by

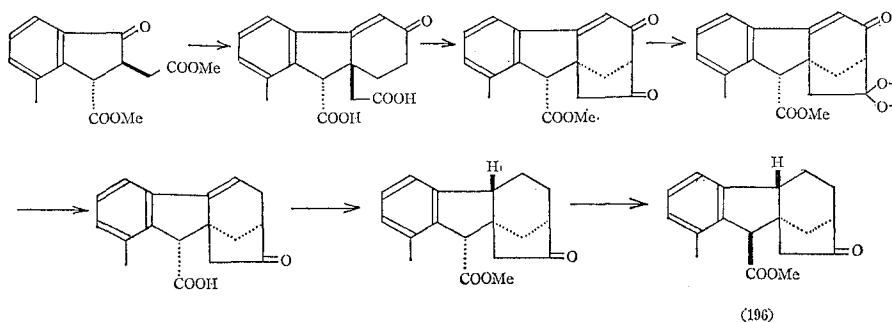
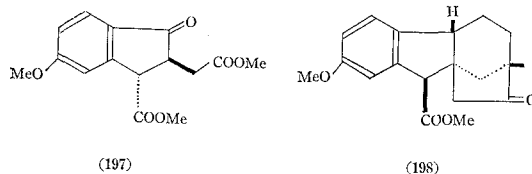


Chart 6

the route shown in Chart 6. Since the indanone **197** was regarded as a key intermediate for the synthesis of the compound **198**, the synthesis of **197** from *m*-methoxy-benzaldehyde and the alkylation of **197** were investigated.<sup>121)</sup>



Geranylgeraniol-2-<sup>14</sup>C was prepared by a modified Wittig reaction and converted to geranylgeranyl-2-<sup>14</sup>C pyrophosphate. An enzyme system from the endosperm of immature seeds of *Echinocystis macrocarpa* catalyzed the cyclization of geranylgeranyl pyrophosphate to *ent*-kaurene. The enzymic activity, which

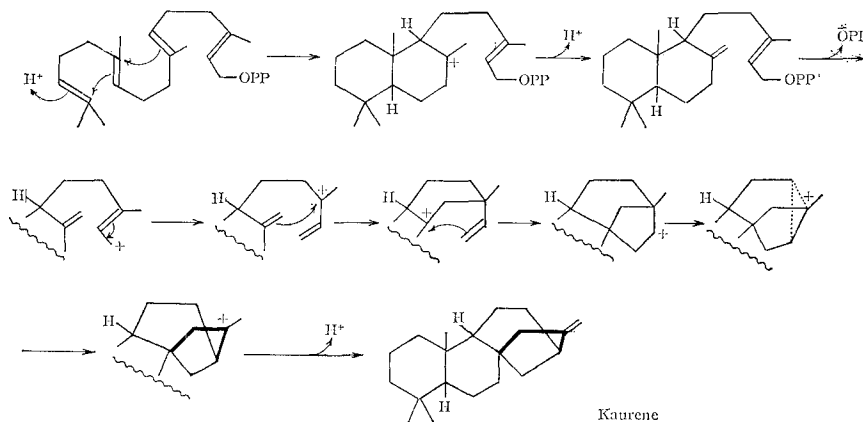
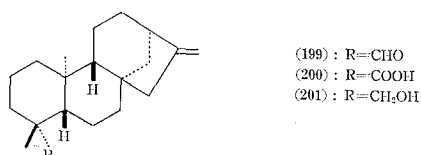


Chart 7

was found in the  $105.000 \times g$  supernatant fraction, was named kaurene synthase. A possible mechanism for cyclization of geranylgeranyl pyrophosphate to *ent*-kaurene was discussed as shown in Chart 7.<sup>122)</sup> *ent*-Kauren-19-al (199) and *ent*-kauren-19-oic acid (200) were identified as products of mevalonate metabolism in an endosperm homogenate of *Echinocystis macrocarpa* (wild cucumber). These products were formed in addition to *ent*-kaurene and *ent*-kauren-19-ol (201), which



were identified earlier. The evidence indicated that *ent*-kaurene is oxidized irreversibly to *ent*-kaurenol, *ent*-kaurenal, *ent*-kaurenoic acid, and a mixture of at least four other unidentified acids, in that sequence, in endosperm homogenates. <sup>14</sup>C-*ent*-Kaurenal was incorporated into gibberellic acid in washed suspensions of *Fusarium moniliforme* cells. This finding, and similar results for kaurene, kaurenol, and kaurenoic acid reported earlier, indicated an intermediate role for all these substances in gibberellin biosynthesis.<sup>123)</sup> A hypothesis of gibberellin biosynthesis in *Echinocystis* endosperm which takes into account the results is shown in Chart 8.<sup>123)</sup>

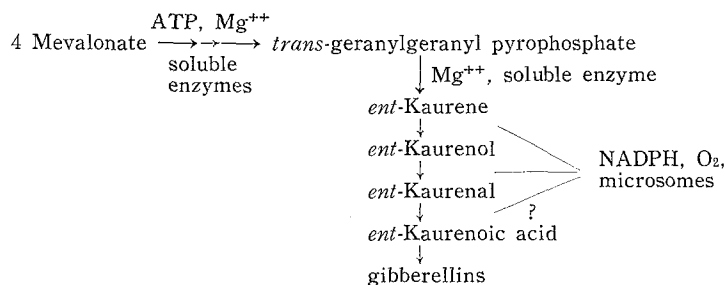
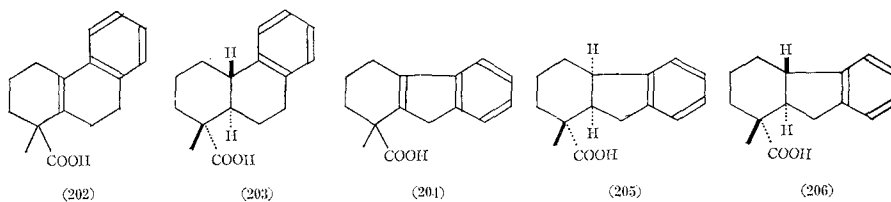


Chart 8

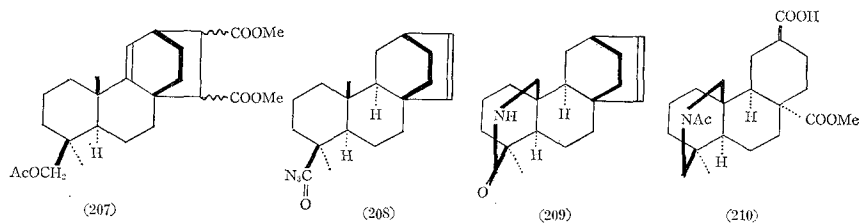
The stereochemistry of lithium-ammonia reduction of cyclic styrenoid systems containing a neighbouring carboxylic acid group was investigated. Compound 202 was converted into 203,<sup>124)</sup> whilst compound 204 was reduced to give 205 (53%) and 206 (23%).<sup>125)</sup>



## X. ATISANE DERIVATIVES

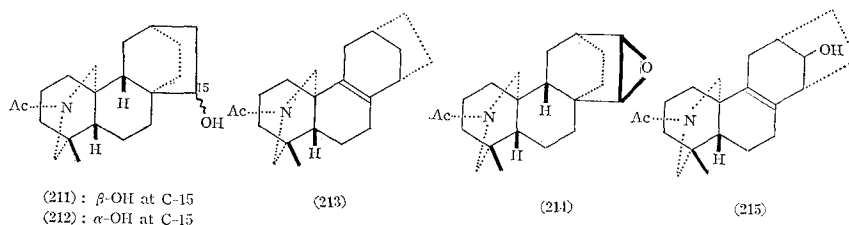
Starting from podocarpic acid, dimethyl ester 207 was derived, which was

converted into lactam **209** via irradiation of **208** by Zalkow *et al.*<sup>126)</sup> The conversion of **209** into **210** which had been converted into atisine<sup>127)</sup> was given up because of the limited amount of **209**.

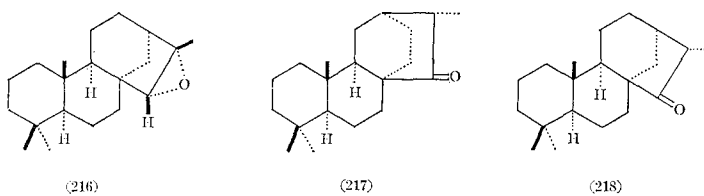


The detailed full paper about the elegant total synthesis of *dl*-atisine was published by Nagata *et al.*<sup>128)</sup>

Skeletal rearrangements of **211** and **212** into **213** were observed by their treatment with  $\text{PBr}_3$ .<sup>129)</sup> Epoxide **214** also showed the same type of rearrangement to

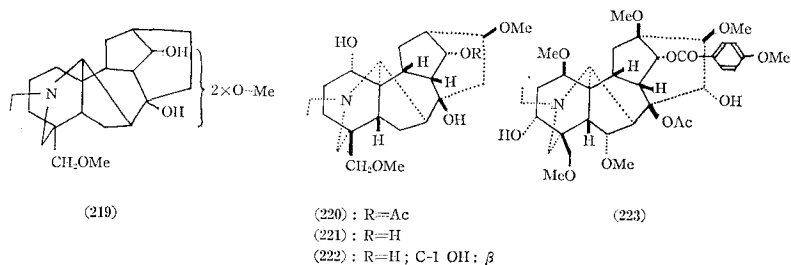


**215.** The transformation of phyllocladene into an atisane-like system was investigated<sup>130)</sup>: epoxide **216** was treated with  $\text{BF}_3$ -etherate to give **217** in addition to ketone **218**.



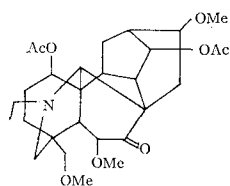
## XI. ACONANE DERIVATIVES

Seven alkaloids were isolated from the root of *Aconitum septentrionale* and characterized. The main alkaloid was lappaconitine and the minor alkaloids

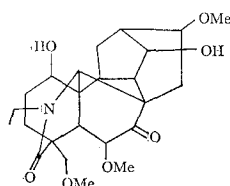


were new except deacetylappaconitine.<sup>181)</sup> A study of *Aconitum variegatum* afforded talatisamine and cammaconine. The partial structure 219 was proposed for talatisamine.<sup>182)</sup> From the root of *Delphinium denudatum*, condelphine (220) and isotalatizidine (221) were isolated. The structure 222 of talatizidine, the C-1 epimer of isotalatizidine, was also clarified.<sup>183)</sup>

The structure 223 of jesaconitine was clarified.<sup>184)</sup> The structures 224 and 225 were assigned to anhydrodiacetyldelcosine and anhydrooxodelcosine.<sup>185)</sup> Glycine-2-<sup>14</sup>C and mevalonate-2-<sup>14</sup>C were incorporated into diterpenoid alkaloids in *Delphinium ajacis*.<sup>186)</sup>



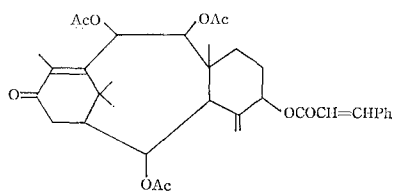
(221)



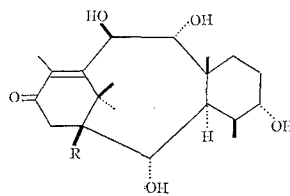
(225)

## XII. TAXANE DERIVATIVES

The structure elucidation of taxicin-II was described in detail by Lythgoe *et al.*<sup>137)</sup> The plane structure 226 was proposed. Subsequently, the full paper on the stereochemistry of taxicin-I and taxicin-II was published. 4, 20-Dihydrotaxicin-I and dihydrotaxicin-II are represented as 227 and 228, respectively.<sup>138)</sup> O-*p*-



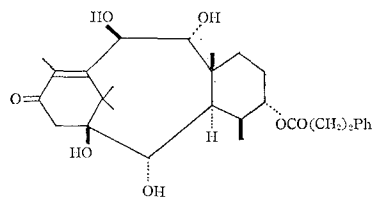
(226)



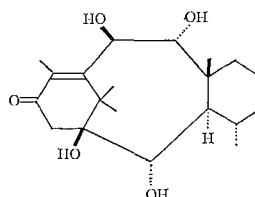
(227) : R=OH

(228) : R=H

phenylpropionyltaxicin-I on hydrogenation on Pd-C catalyst in ethyl acetate gave dihydro derivative 229, while the former on the same treatment in aqueous methanol gave a hydrogenolyzed product 230 accompanied by 229.<sup>139)</sup> From the

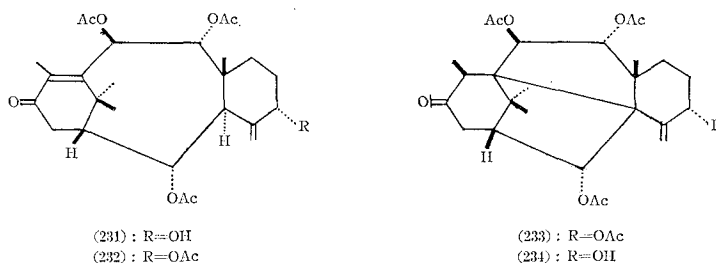


(229)



(230)

leaves of *Taxus cuspidata*, four new diterpenoids, that is, Taxinin A (231), T-H (232), T-L (233), and T-K (234) were isolated and their structures were elucidat-

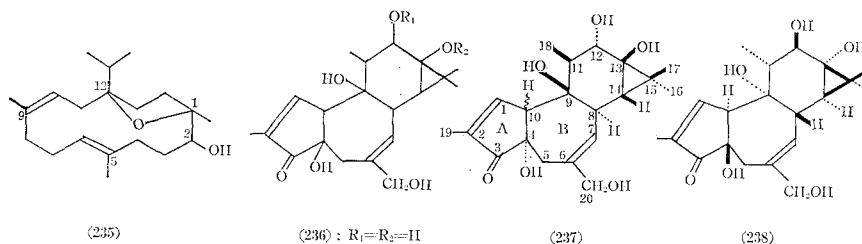


ed.<sup>140)</sup> The structure of T-K was established by discovery that irradiation of T-A in dioxan for 15 minutes with a 450 W high-pressure Hg-lamp produced T-K in more than 15% yield. Mechanistic considerations suggested that the 12-methyl has the  $\beta$ -configuration.<sup>140)</sup>

### XIII. THE OTHERS

As one of the neutral components of frankincense (produced by *Boswellia carteri*), a new macrocyclic diterpene, incensole was isolated. The structure was shown to be 12-isopropyl-1, 5, 9-trimethyl-1, 12-oxido-5, 9-cyclotetradecadien-2-ol (235).<sup>141)</sup>

Active investigations about the chemistry of phorbol, a novel diterpene from *Croton* oil (seed oil of *Croton tiglium*) were carried out by Hecker *et al.* Preliminary acetylation,<sup>142)</sup> dehydration and dehydrogenation<sup>143)</sup> experiments led to an assumption that phorbol has a hydroazulene skeleton. The reaction of the alcoholic hydroxy groups in phorbol with diazomethane in the presence of aluminum isopropoxide was investigated to afford ethers.<sup>144)</sup> On the basis of the periodate- and lead tetraacetate-oxidations, the partial structure of phorbol was proposed.<sup>145)</sup> Phorbol diacetate was oxidized to give a diketone, phorbolone, whose circular dichroism was investigated.<sup>146)</sup> Eleven irritant and tumor promoting compounds have been isolated and purified from *Croton* oil. All eleven compounds isolated were diester of one and the same alcohol phorbol  $C_{20}H_{28}O_6$  (236), each diester containing one short chain and one long chain fatty acid.<sup>147)</sup>

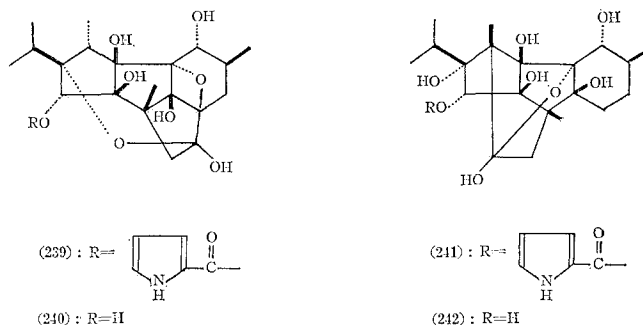


Structure and stereochemistry of phorbol were elucidated as shown in 237. Hecker *et al.*<sup>148)</sup> proposed the name tiglian for saturated parent hydrocarbon with the same configuration at those asymmetric centers, and the x-ray analysis<sup>149)</sup> of 5-bromofuroate derivative of phorbol established the structure and relative configuration of phorbol, which clarified A/B trans juncture in 237. Subsequently,

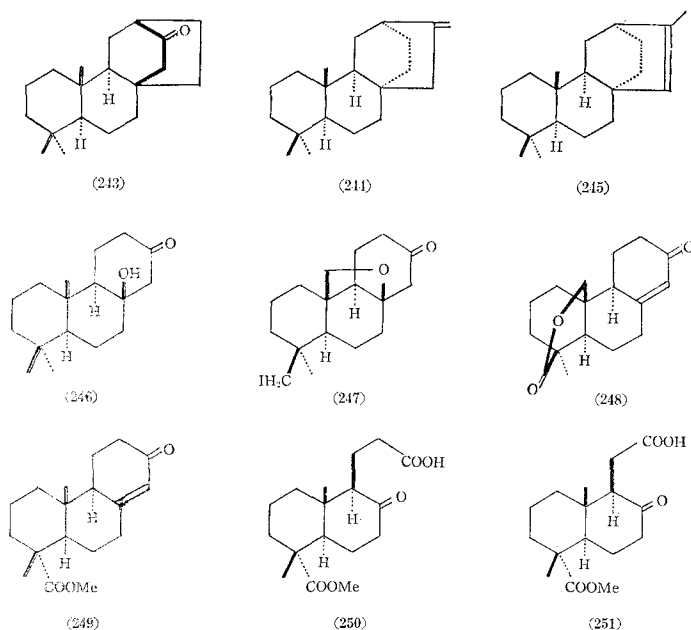


however, the x-ray analysis<sup>150)</sup> of neophorbol-13,20-diacetate-3-*p*-bromobenzoate confirmed the absolute configuration of phorbol to be shown as 238.

Wiesner *et al.*<sup>151)</sup> revised their previously proposed structures<sup>152)</sup> 239 and 240 for ryanodine and ryanodol to 241 and 242, respectively, on the basis of some chemical reaction.



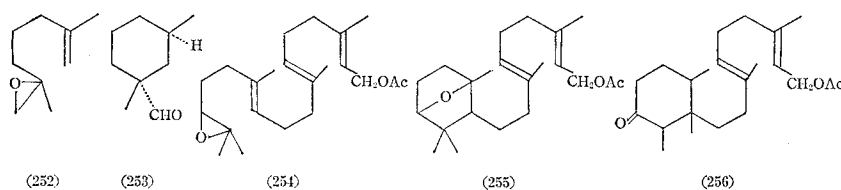
Maleopimaric acid was converted into ketone 243, which was transformed into *anti*-neoatisirene (244) and *anti*-neoisoatisirene (245).<sup>153)</sup> Wenkert and Mylari<sup>154)</sup> derived 246 from manool, and treated it with lead tetraacetate and iodine. One of the products, 247, was treated with NaHCO<sub>3</sub> in DMSO to give a mixture



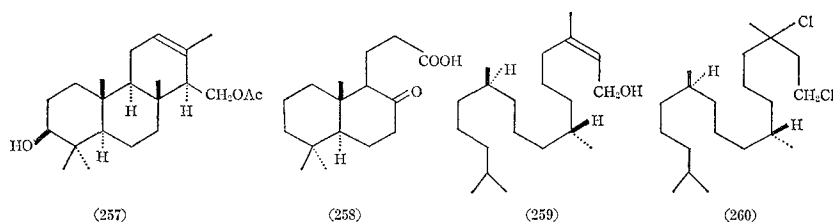
of hemiacetals accompanied by other products. From the mixture of hemiacetals upon Jones oxidation there could be isolated an enone lactone 248, which may be a potential intermediate for syntheses of diterpenes of *Sciadopitys verticillata* and diterpene alkaloids.

Three resin acid degradation products, 249, 250, and 251, were synthesized.<sup>155)</sup> A synthesis of geranylgeraniol-2-<sup>14</sup>C was reported.<sup>156)</sup> Whalley *et al.* published a

series of reports on the chemical shift, in which long-range effects of methyl groups and the anisotropies of the C-C and C-H bond<sup>157)</sup>, the anisotropies of the carbon-carbon double bond,<sup>158)</sup> and the NMR spectra of some diterpenes<sup>159)</sup> were described. The chemical shifts for the C-17, C-19, and C-20 methyl groups in the resin acids and their hydrogenated derivatives were calculated and the methyl resonances assigned. Mass spectrometric studies of aromatic diterpenes were published.<sup>160)</sup> Klyne and Crabbé<sup>161)</sup> described ORD and CD of aromatic diterpenes in their general survey. Gaschromatography and mass-spectrometry of the trimethylsilyl ether of vitamin A and some of its isomers were reported.<sup>162)</sup> As a model for synthesis of ring A of the diterpene acids, the cyclization of epoxyolefin 252 was tried to give an aldehyde 253.<sup>163)</sup> Geranylgeranyl acetate terminal epoxide (254) was cyclized by its treatment with stannic chloride in benzene to

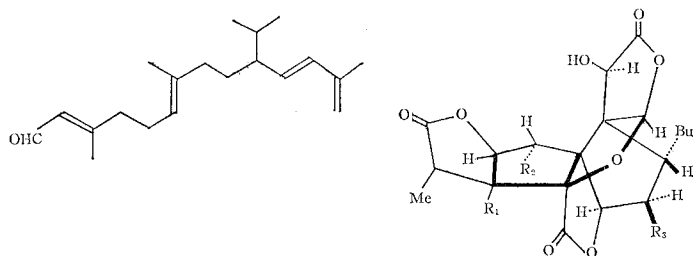


give 255~257 and acyclic terminal chlorohydrin.<sup>164)</sup> The new synthesis of a potential intermediate 258 which is useful for the synthesis of diterpene was carried out.<sup>165)</sup> From the essential oil of the leaves of *Chamaecyparis taiwanensis*, a diterpene was isolated.<sup>166)</sup> So-called "dundatholic acid" from *Agathis robusta* oleoresin was investigated and it was proved that this is a mixture of abietic acid, neoabietic acid, *trans*-communic acid, and *cis*-communic acid, with other unidentified acids.<sup>167)</sup> Saturated hydrochloride 260<sup>168)</sup> was prepared from phytol (259) and HCl. Virescenol A, a metabolite of *Oospora virescens*, was characterized and its functional groups were shown.<sup>169)</sup>



Geranylgeraniol was first isolated from the wood of *Cedrela toona*.<sup>170)</sup> In the fruit of *Pterodon pubescens*, all-*trans*-( $-$ )-14, 15-epoxygeranylgeraniol and geranylgeraniol were recognized and isolated.<sup>171)</sup> A new C<sub>20</sub>  $\alpha$ ,  $\beta$ -unsaturated aldehyde 261 was found from Tobacco.<sup>172)</sup>

Nakanishi *et al.* isolated and characterized various kinds of ginkgolides, the bitter principles of *Ginkgo biloba*,<sup>173)</sup> and proposed their partial structures.<sup>174)</sup> Subsequently, the structure 262 of ginkgolide A(GA) was proposed.<sup>175)</sup> The stereochemistry of ginkgolides was investigated and their absolute configuration was deduced from the positive Cotton effect in the RD curves of 7-oxo-ginkgolide C monomethyl ether and the F-nor ketone derived from monoacetyldianhydro-



(261)

(262) :  $R_1=OH$ ;  $R_2=R_3=H$  (GA)(263) :  $R_1=R_2=OH$ ;  $R_3=H$  (GB)(264) :  $R_1=R_2=R_3=OH$  (GC)(265) :  $R_1=H$ ;  $R_2=R_3=OH$  (GM)

ginkgolide C monomethyl ether. Thus, the full structures of four ginkgolides, A, B, C and M are summarized<sup>(176)</sup> in 262 to 265, respectively. An independent X-ray study<sup>(177)</sup> of mono-*p*-bromo-benzoate of ginkgolide A arrived at identical conclusions regarding the structure of GA. Some aspects of the NMR spectra of ginkgolides were described including the intramolecular nuclear Overhauser effect.<sup>(178)</sup>

A detailed paper on ginkgolides A, B, and C by Okabe *et al.*<sup>(179)</sup> was independently reported.

A review on the chemistry of  $C_{20}$  diterpene alkaloids was published by Pelletier.<sup>(180)</sup>

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